THERUS.007C1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Weng, et al.
Appl. No.	:	10/633,726
Filed	:	August 4, 2003
For	:	CONTROLLED HIGH EFFICIENCY LESION FORMATION USING HIGH INTENSITY ULTRASOUND
Examiner	:	Eleni M. Mantis Mercader
Group Art Unit	:	3737

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I declare and state as follows:

1. I am a joint inventor of the invention claimed in the above-captioned patent application.

2. During the time period in which I participated in the events and activities described herein, I was employed by Therus Corp., the assignee of the above-captioned application.

3. All of the events and activities described herein were performed by me personally, by others at my direction, or by the other joint inventors, as part of our duties as employees of Therus, Corp.

4. The invention claimed in Claims 10-14 in the above-captioned patent application was conceived prior to September 17, 1999 and activities to diligently reduce it to practice and file it in the U.S. Patent and Trademark Office were pursued thereafter as described below.

5. Prior to September 17, 1999, I had conceived cutting off the blood supply to a uterine fibroid by selecting a tissue treatment site to which focused high intensity ultrasound energy could be applied to reduce blood supply to the fibroid. Attached in Exhibit A are four laboratory notebook pages copied from one of my laboratory notebooks that I kept as part of my duty as an employee of Therus, Corp., from which the dates have been redacted. These notebook pages were written by me prior to September 17, 1999. The pages are dated and signed by me. On page 46 of my notebook, I described in the last three lines a device that "creates thermal necrosis in the tumor base" of a uterine fibroid. I stated that "[t]he heated tumor tissue shrinks and chooks of [sic] the blood vessels feeding the tumor." On page 47 of my notebook, I described partitioning the base of the tumor into several sectors and then providing a heating zone in each sector to create a wedge of tissue necrosis that would result in the cutting "off of the tumor blood supply." Accordingly, prior to September 17, 1999, I had conceived the invention set forth in Claim 10 of the above-identified application and the additional limitation added to Claim 11 by dependent Claim 14.

6. At least by September 17, 1999, I had conceived determining a tissue treatment zone and then energizing an ultrasound transducer to cause pre-focal heating and necrosis at the tissue treatment zone. On page 47 of my laboratory notebook, I describe partitioning a tumor base into several sectors (Exhibit A). A "wedge-shaped heating zone" is then applied to each sector to "create a wedge of tissue necrosis." Accordingly, I described determining a tissue treatment zone and energizing an ultrasound transducer to cause tissue necrosis as claimed in Claims 11-13. On page 45 of my notebook, I described the advantage of "pre-heating of...intermediate tissue." Similarly, on page 46, I discussed raising "the temperature in the pre-focal zone" and using HIFU transducers to "directly heat[] the intermediate tissue." On page 47 of my notebook, I depict a "heating zone" in the pre-focal area. Accordingly, I described causing pre-focal heating as claimed in Claims 11-14. Therefore, prior to September 17, 1999, I had conceived of the invention set forth in Claim 11 of the above-identified application.

7. On page 45 of my notebook, I stated that "[t]issue acoustic absorption increases significantly when tissue temperature rises above 50° C" (Exhibit A). Accordingly, prior to

September 17, 1999, I had conceived the invention set forth in Claim 12 of the above-identified application.

8. On page 45 of my notebook, I note that "[p]re-heating of the intermediate tissue becomes an advantage to reduce the treatment time.. Instead of pulsed ultrasound, highly efficient and effective continuous-wave (cw) ultrasound can be used to heat the tumor tissue rapidly in a large volume to cause tissue necrosis" (Exhibit A). I also state on page 45 that "[i]t is the seed to start the above positive feedback heating process to efficiently necrose the tissue volume." Accordingly, prior to September 17, 1999, I had conceived the invention set forth in Claim 13 of the above-identified application.

10. Attached in Exhibit B are pages 54 and 55 of my laboratory notebook, from which the dates have been redacted. These notebook pages were written by me prior to September 17, 1999. The pages are dated and signed by me. These pages document the continuing diligent effort by me to reduce the claimed invention to practice.

11. After having conceived the claimed invention, I timely provided an invention disclosure to the patent attorney for Therus Corp. at the time, Jeffery Slusher, so that he could prepare and file the application to which the above application claims priority. The invention disclosure without the attached laboratory notebook pages is attached in Exhibit C. Based on information and belief, the application was diligently prepared and filed. The invention disclosure is dated and signed by me. The dates have been redacted. The invention disclosure demonstrates further diligent effort by me to reduce the invention to practice. In addition to describing my invention, the invention disclosure describes experimental studies of creating thermal lesions.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful statements may jeopardize the validity of thc application or any patent issued thereon.

By: ______________________ Date: Sept. 18, 2005
Lce Wcng

1853792
081505

Exhibit A

Ultrasound Tissue Ablation Devices for Minimum Invasive Surgery (MIS)

△ The Need

During laparoscopic MIS, such as Myomectomy for uterine fibroid removal, the difficulty is not the tumor removal but the uterine repairment (sutering) after the tumor is removed. Suturing under laparoscope requires very experienced skills. It is also very time consuming. Improperly repaired uterus may cause adhesion after the surgery and uterine rupture during later pregnancy.

Besides suturing, bleeding control is another difficulty in MIS. During laparoscopic myomectomy to remove multiple uterine fibroids, blood loss is usually a significant problem. Oftentimes, blood transfusion is required.

These technical difficulties limit the wide adoption of MIS in many surgical procedures. It is desirable to have an MIS tool which distroys the tumor without incision and bleeding at the organ. A non-invasive or minimum-invasive tool at the organ level for the MIS procedures will provide many benefits to the surgeons and the patient, and will help MIS become a more widely accepted procedure.

△ The Technology

High-Intensity Focused Ultrasound (HIFU) has been studied for years for generating isolated thermal lesions at a controlled depth near its focus. Thermal lesion of large volume can be created by scanning the focus electronically or mechanically in the tissue.

To create a large-volume lesion inside an organ, we normally turn the ultrasound on for 1-3 seconds to generate a small lesion, move the ~~trans~~ ultrasound focus to an adjacent location, wait 40-60 seconds for the intermediate tissue ~~to~~ between the ~~tr~~ transducer

(continue's)

and its focus to cool down. then turn the ultrasound power on again to creat one more small lesion. This scanning and pausing process can be very slow. It may last very long time (~ 4 hours) to treat a relatively small volume of tumor (~ 1 cubic inch). This long procedure time may not be practical in clinical.

The main reason of the long treatment process is to pause between each ultrasound pulse to avoid thermally damaging the intermediate tissue. But in many situations, the tumor is superficial at the organ surface, such as subserosal fibroid. In these cases, the pausing becomes unnecessary, if we can bring the treatment transducer in direct contact to the tumor. Pre-heating of the intermediate tissue ~~beco~~ becomes an advantage to reduce the ~~procedure~~ treatment time. Instead of pulsed ultrasound, highly efficient and effective continuous-wave (CW) ultrasound can be used to heat the tumor tissue rapidly in a large volume to cause tissue necrosis. In an ex-vivo study, ~~a volume of~~ liver tissue ~~ab~~ of ~½ cubic inch in volume was completely necrosed in 1 minute.

How to turn pre-heating from a disadvantage to an advantage has not been thoroughly studied in published literature. Tissue acoustic absorption increases significantly when tissue ~~temperature~~ rises ~~abov~~ above 50°C. There is a ~~pos~~ possitive feedback process in tissure heating.

Tissue temperature ↑ ⟹ tissue absorption ↑

more acoustic energy converts to heat

~~Tissue~~ For a small F-number (~1.8) HIFU transducer running in CW mode, tissue temperature at its focus will rise to 70–80°C in less than 2 seconds. This hot spot with high absorption serves two purposes:

① It is the seed to start the above positive feed back heating process to efficiently necrose the tissue volume;
② Its high absorption blocks ultrasound energy from damaging tissue beyond the focus.

(continues)

If ~~thermally~~ effectively necrose the tissue between the transducer and its focus is the purpose, some of the conversional wisdoms in HIFU may need modifications. Following is a list of findings from ex-vivo experiments.

① For a given depth of treatment, a higher ultrasound frequency can be used to achieve faster treatment in tissue volume.

② Transducer F-number becomes a less critical issue. It usually takes longer time to raise the temperature in the pre-focal zone, even when F-number changes. In tissues near the transducer, the temperature rise is more or less independent from the F-number, and dependent on transducer surface intensity and frequency.

③ For HIFU transducers directly heating the intermediate tissue, it should have the capability of outputting high power from a small transducer surface. This may requires special transducer material and design. It is less an issue in conventional HIFU design.

④ Transducer surface temperature should be kept low. When the transducer is in direct contact with the treated tissue, if its surface temperature is high, the superficial tissue will be burned first. The thermally necrosed tissue has very high acoustic attenuation. It will block the ultrasound penetrating into deeper tissue. The result is incompleted volumetric tissue necrosis. This is not a problem in conventional HIFU, where the transducer is typically ~~contact~~ not in direct contact with tissue and is cooled by ~~coupling~~ water.

△. The Device

Here are two examples of ~~an ultrasound~~ HIFU MIS devices for uterine fibroid ablation and embolization.

① Device for treating subserosal fibroids.

This device creats thermal necrosis in the tumor base. The heated tumor tissue shrinks and chocks of the blood vessels feeding the tumor to

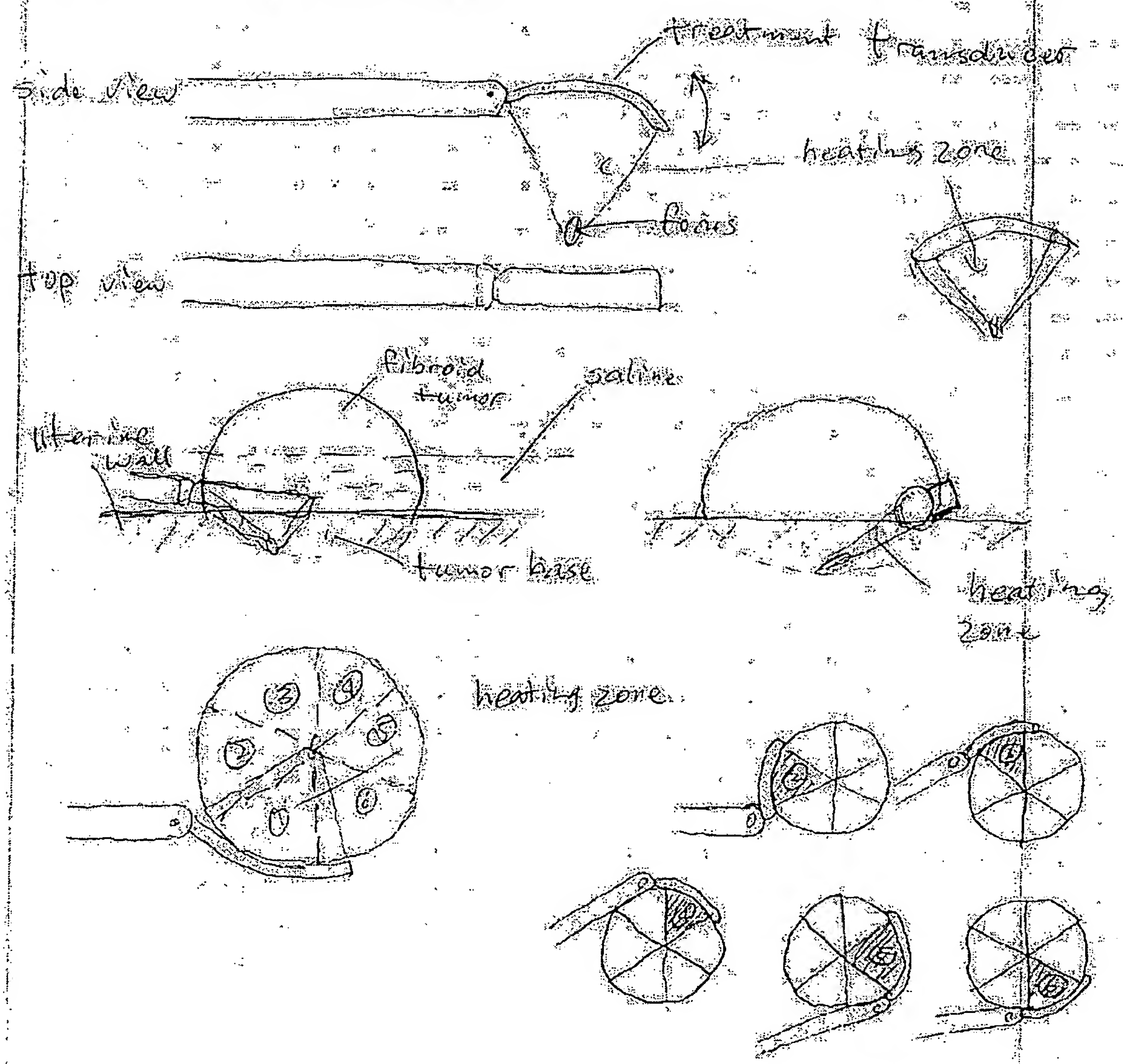
Continuing [redacted]

Witnessed [redacted]

[redacted]

(continues)

embolize the tumor.



The ~~uterus~~ tumor base is partitioned to several sectors. The device generates a wedge-shaped heating zone in each sector. The wedge heating zone (like an invisible "shoval" head) creat a wedge of tissue necrosis deep into the tumor base. ~~After all of~~ the sectors are treated, the tissue shrinkage at the tumor base cuts off the tumor blood supply

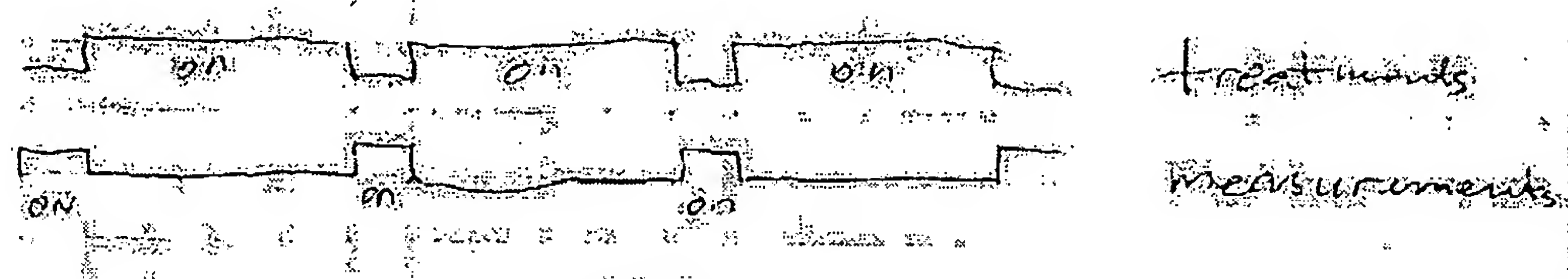
Effect of the treatment is very similar to the thermal necrosis effect caused by myolysis with bipolar

Witnessed [redacted]

Exhibit B

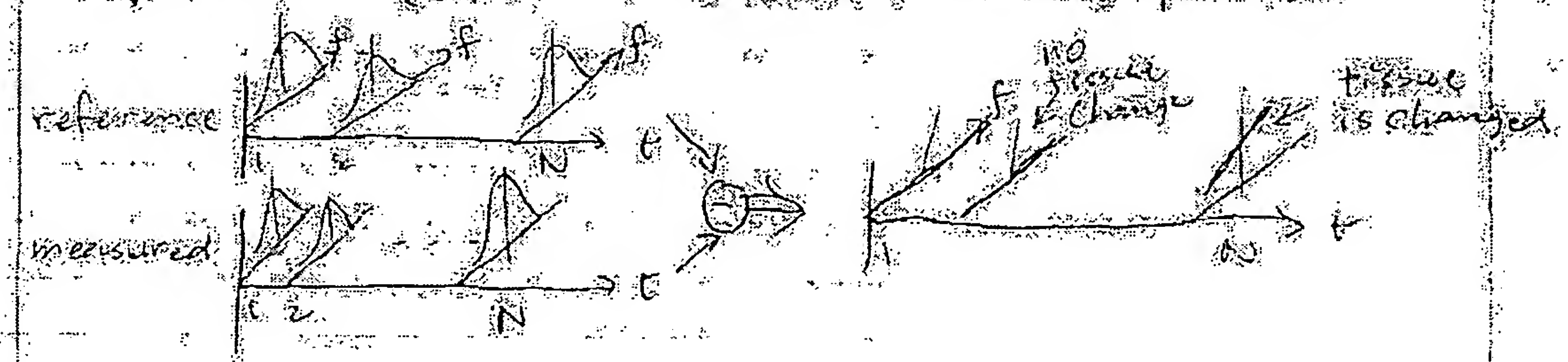
Lee Wang [redacted]

(continue's)
During the HIFU treatment, the ~~xx~~ spectrum measurements are taken periodically to monitor the spectrum change. The ~~treatment~~ and the measurement are interleaved (d.)



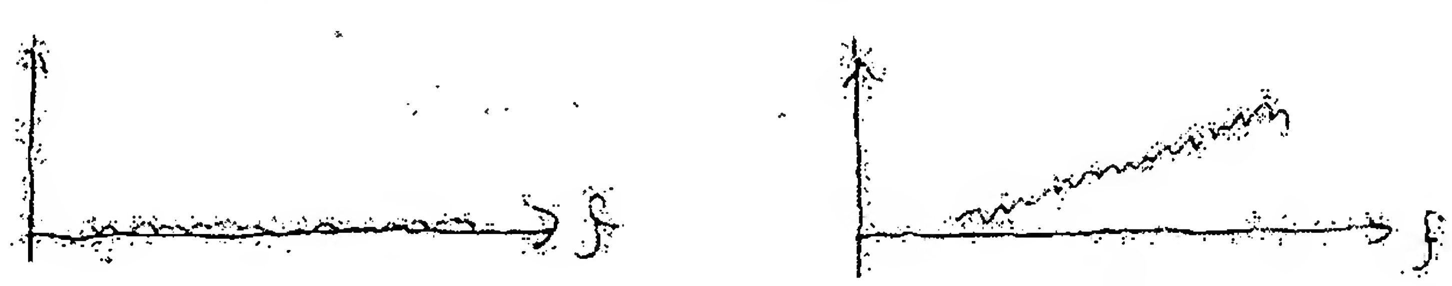
(d)

In each ~~[illegible]~~ measurement, the spectrum at a certain depth t is subtracted from the reference spectrum (e). The result is the spectrum



(e) (f)

difference at the depth (f). If tissue at the depth has not been necrosed, the spectrum difference should be very small over all frequency range f (g). If the spectrum difference is significantly different from zero, especially at the high frequency end, the tissue at the depth is necrosed. ~~The~~ Necrosed tissue has ~~higher~~ larger slope of attenuation coefficience β. ~~Attenuation of soft tissue is~~
More high frequency components are attenuated than the low frequency component. The ~~result~~ result is a ~~non-zero~~ spectral ~~of~~ ramp (h).



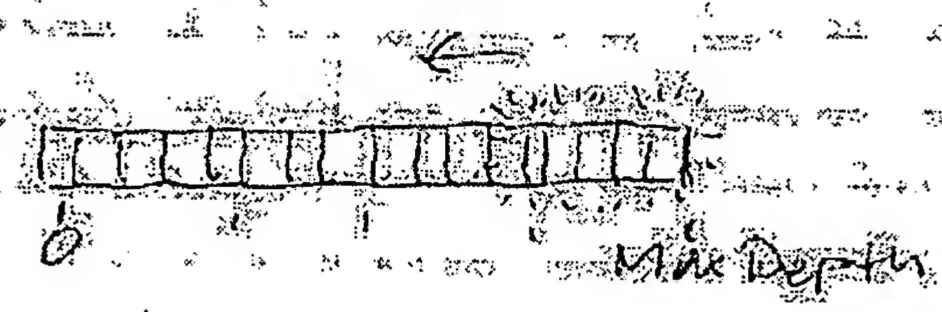
(g) (h)

Lee Wang [redacted]
6/14/2001 W Peng [redacted]

[redacted]

(Continue's)

By monitoring the spectral changes, we obtain the real-time information of the tissue necrosis process from the focus moving towards the transducer. The result can be displayed with a LED array ~~which~~ ~~is~~ of which the LED's are lighting on sequentially from deeper to shallower depth during the treatment. (i)



(i)

witnessed [redacted]

Exhibit C

Therus # 0899-05

INVENTION DISCLOSURE Therus FILE No. LW010__ COVER PAGE

The below-described invention(s) was conceived on [redacted] by the following inventor(s): Lee Weng

TITTLE: **Method and Apparatus for Efficiently Heating Biological Tissues with Ultrasound**

BACKGROUND AND SUMMARY PURPOSE:

High-Intensity focused ultrasound (HIFU) has been used to ablate deep tumor and other tissue non-invasively. Under HIFU, tissue temperature at the ultrasound focus can rise to 70-90 degree-C in a few seconds. This high temperature causes tissue necrosis in the tumor. It can also coagulate the tumor tissue and destroy the blood supply to the tumor. When blood vessels of the tumor are embolized, the tumor will die.

One disadvantage of the current HIFU therapy is its inefficiency when treating large tumors or heating large volume of tissues. Even though a 3-second ultrasound pulse can increase the temperature at its focus dramatically, the ultrasound treatment must pause 40-60 seconds between two subsequent pulses to cool down the intermediate tissue between the focus and the ultrasound transducer to avoid thermally damaging the tissue. The volume of tissue necrosis for each treatment pulse is very small (~0.05 cubic cm). To treat a volume of tissue in a medium size of 1 cubic inch, it will take more than 4 hours, which are too long to be practical in most clinical situations. In this case, the average treatment rate is about 0.05 cm3/min.

Many tumors are at superficial or outside of the organ, such as subserocial and some intramural fibroid tumors in uterus. During laparoscopic surgeries, surgeons can easily reach the surfaces of those tumors with a laparoscopic instrument. If we can put a HIFU transducer at the tip of a laparoscopic instrument and let the transducer touch the tumor directly, there will be no intermediate tissue that needs to be spared and cooled, so that the pauses in the treatment may become unnecessary.

SUMMARY BENEFITS OF THE INVENTION:

Different from the conventional wisdom, where the prefocal heating is considered as a negative effect and needs to be cooled, I realize that the prefocal heating can provide significant enhancement to the efficiency of tissue heating, if the HIFU transducer can directly contact the tumor surface. The positive feedback mechanism of the heating enhancement is described in Page 45 of the attached notebook copies. In an experimental study, a wedge-shaped lesion of tissue necrosis was generated with this mechanism by running the ultrasound power continuously while keeping the transducer position fixed. The volume of the thermal lesion was about 4.5 cubic cm. The treatment time was 2 minutes. The average treatment rate was about 2.25 cm3/min, which was 45 times faster than the conventional pulse-pause treatment strategy. The treatment time can be further reduced to 1 minute with some improvements of the ultrasound transducer.

The large thermal lesion starts from a small isolated lesion at the transducer focus. With the highest ultrasound intensity at the focus, this small lesion is generated in a few seconds. The small lesion serves at the initial seed to start the positive feedback process. Necrosis tissue of the small lesion has much higher acoustic attenuation than the normal tissue, so that the small lesion blocks prevents the ultrasound energy from penetrating beyond the focal depth to cause undesirable tissue damage.

It was found in an experiment study that after the lesion started at the focus, it was first growing along the central axis of the transducer and moving towards the transducer to form a long lesion. Then the end of the long lesion closer to transducer started growing wider laterally and eventually the lesion became a wedge shape. The tissue layer near the surface was the last part turned necrosis.

Signatures: Inventor(s): date: [redacted]

Witnessed and Understood: date: [redacted]

We can control the size and the shape of the large thermal lesion. If we want to form a thin and long lesion column in the tissue, we should use a circular transducer with a relatively large F-number (~2) and treat the tissue in a relatively short time. To crea[redacted]l shaped lesion, we should use a circular transducer with a small F-number (~1) and treat the tissue in a relatively long time. To form a wedge-shaped lesion with thin thickness, shaped like a slice of pie, we should use a cylindrical or truncated circular transducer and treat the tissue in a relatively long time. We can generate a rectangular lesion plane by forming a row of tightly spaced lesion columns. Each column is formed with a fixed transducer position in a short time. Then transducer quickly moves one step laterally and generates the next adjacent column. Thermal diffusion in the tissue fuses the columns together to become a rectangular plane.

We can also create a large lesion in the tissue without damaging the organ surface. Using the attenuation measurement technique described in Page 52-55 of the attached notebook copies, we can monitor the lesion growth during the treatment. When the lesion growth reaches the desired depth, the system can turn the ultrasound power off automatically.

DESCRIPTION OF THE INVENTION:

Using this positive feedback treatment method, we can design a laparoscopic ultrasound device for minimum-invasive surgery (MIS) to rapidly treat tumors and other pathologies inside the abdomen. Essentially, this device has a HIFU treatment transducer at the end of a long bar that can be inserted into the abdominal cavity through a trocar in the abdominal wall. The transducer surface has a narrowly truncated cylindrical or spherical shape. The transducer focuses ultrasound in the tissue. The transducer can swing around the tip of the bar to point the ultrasound beam in different directions for different treatment angles.

This device can be used to treat uterine fibroids. Detailed descriptions are in the attached notebook Page 46-50. For treating a subserosal fibroid, the surgeon can apply the device to the tumor base. The tumor tissue at its base will be thermally coagulated sector by sector around. Under high temperature, tissue shrinkage at the base will shut off the blood supply to the entire tumor and cause its later death. For an intramural fibroid, the device can be used to debulk the tumor by creating multiple large lesions inside the tumor. The treatment result is very similar to the result of Myolysis, where laparoscopic bipolar RF needles are inserted in the tumor 5-100 times to coagulate the tumor. Comparing to Myolysis, the proposed ultrasound treatment has advantages in non-invasiveness to the tumor, easiness of operation, fast treatment, and less risk of post-operative adhesions.

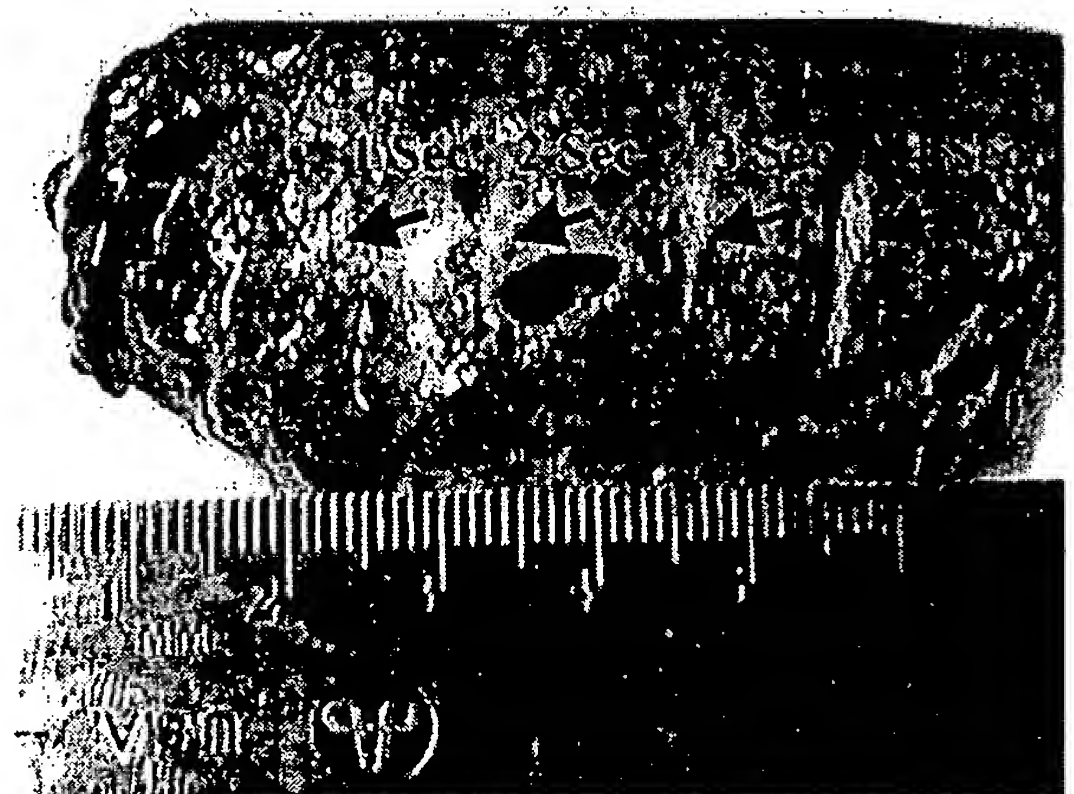
Some detailed features of the device are described in Page 50-55 of the attached notebook copies. These features include designs to keep the transducer cool, designs to achieve high ultrasound output, and designs of treatment control.

[redacted]

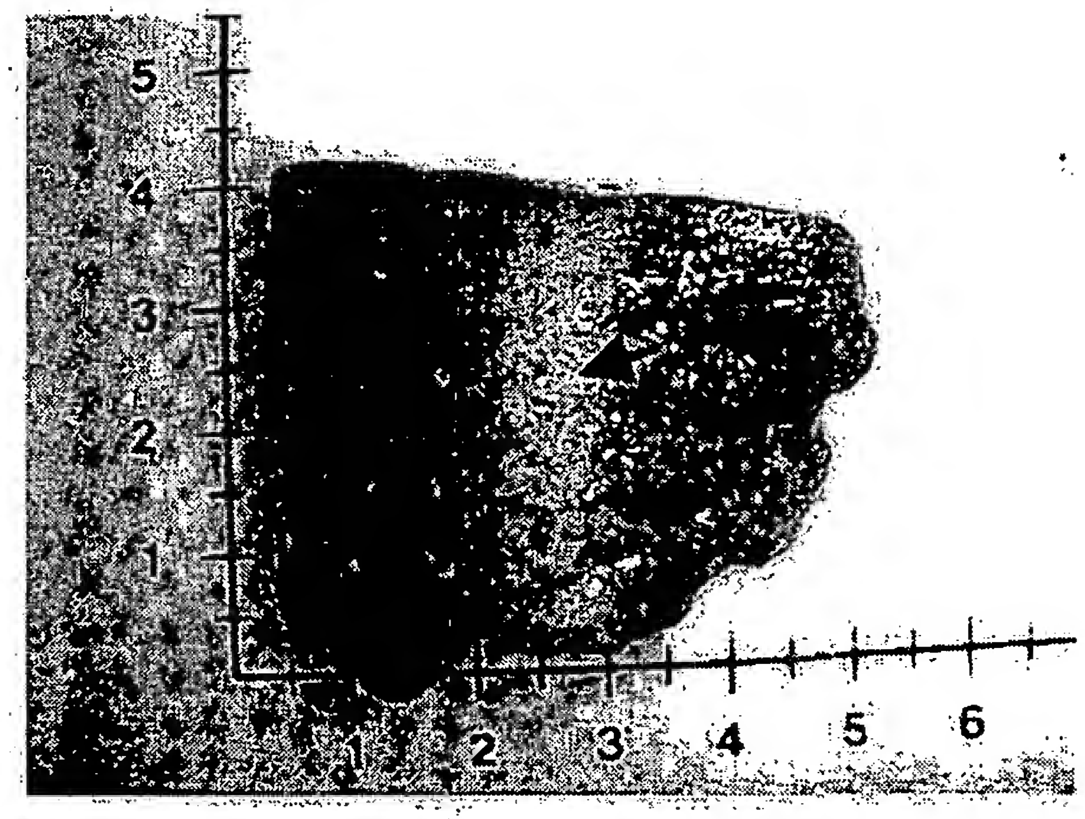
Signatures: Inventor(s): date:

Witnessed and Understood: [redacted]ate:

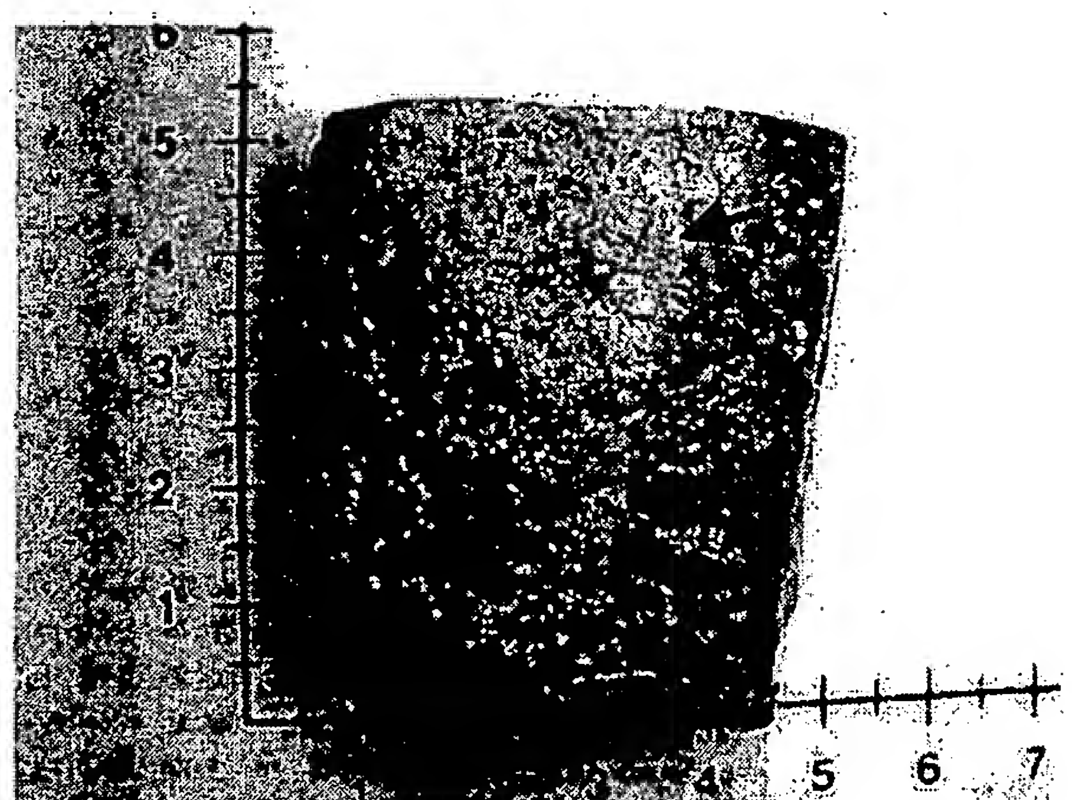
Controlled Thermal Lesions in Liver



Isolated Lesions at Controlled Depth



Column



Wedge

Plane

witnessed [redacted]

Page 3 of 17

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witnessed [redacted]

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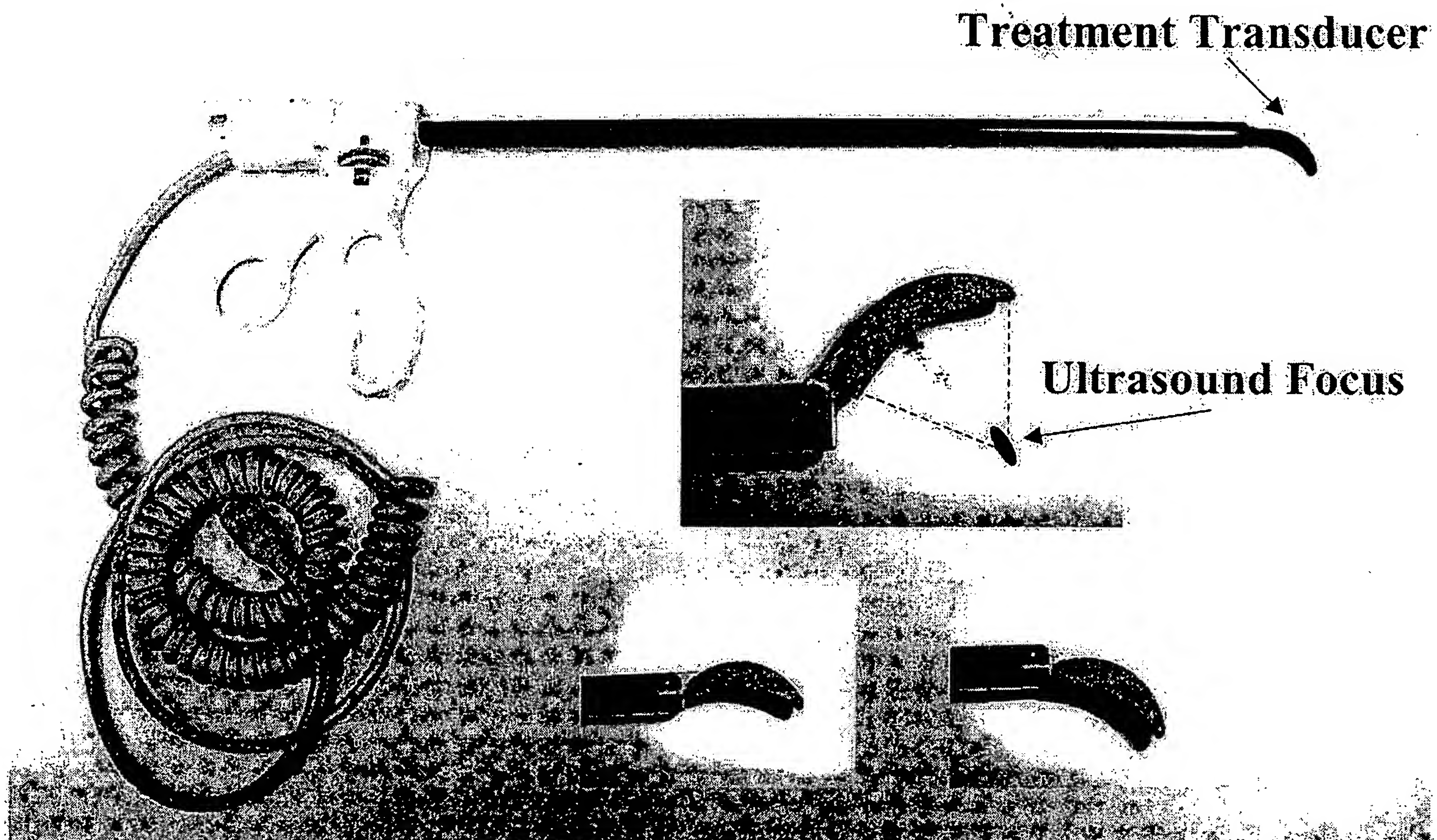
Ultrasound MIS Tool

(A Conceptual Model)



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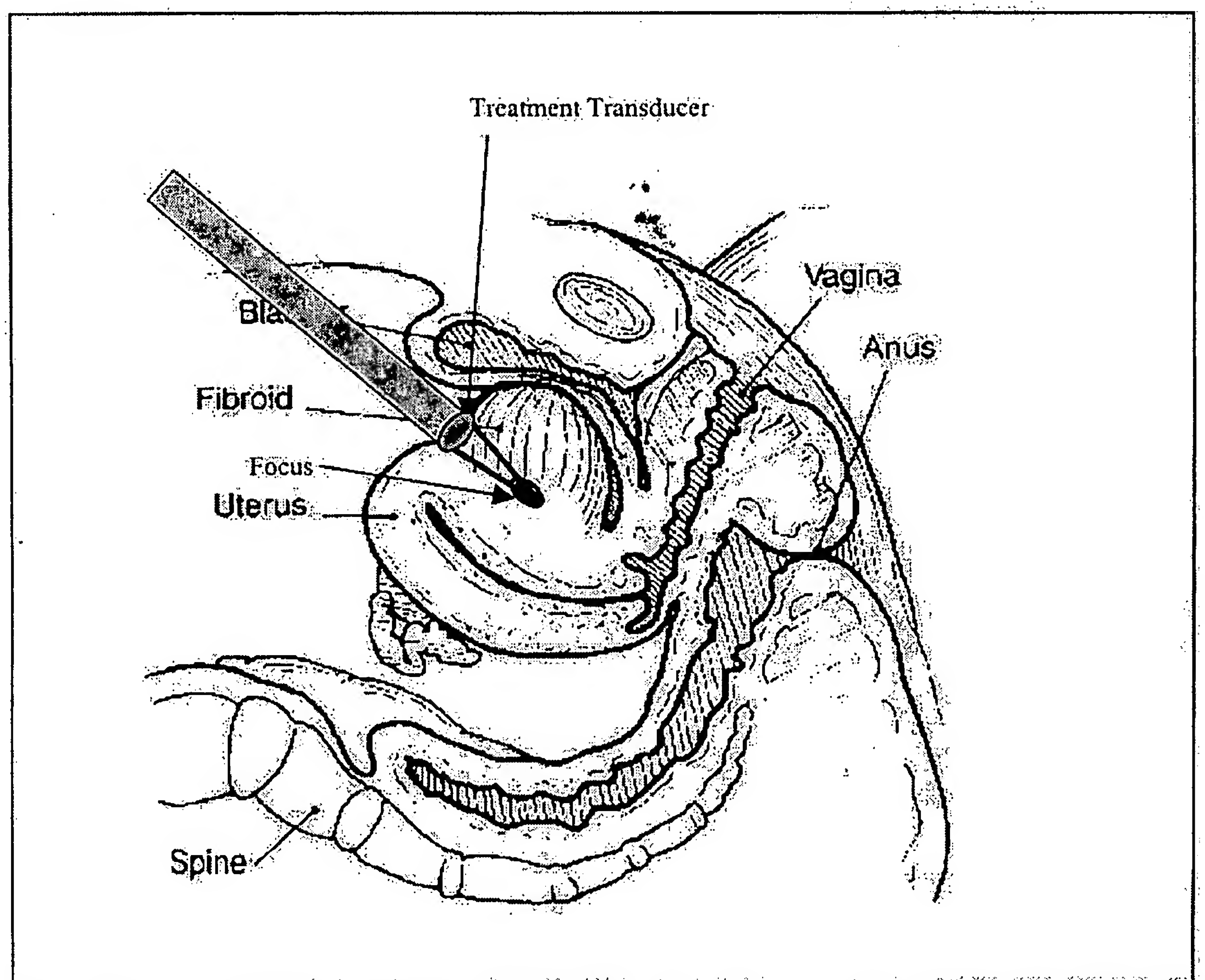
Uterine Fibroid Ablation

(Laparoscopic Approach)



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